

Decompensation in a 51-year-old woman with schizophrenia

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Ms. A, age 51, has schizophrenia that for years had been stabilized with haloperidol. She recently became agitated and refuses to take medication. What could be causing these changes?



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CASE Psychotic and reclusive

Ms. A, age 51, has schizophrenia and has been doing well living at a supervised residential facility. She was stable on haloperidol, 10 mg twice a day, for years but recently became agitated, threatening her roommate and yelling during the night. Ms. A begins to refuse to take her haloperidol. She also refuses to attend several outpatient appointments. As a result, Ms. A is admitted to the psychiatric unit on an involuntary basis.

In the hospital, Ms. A rarely comes out of her room. When she does come out, she usually sits in a chair, talking to herself and occasionally yelling or crying in apparent distress. Ms. A refuses to engage with her treatment team and lies mute in her bed when they attempt to interview her. Her records indicate that previous medication trials have included chlorpromazine, fluphenazine, haloperidol, paliperidone, ziprasidone, and quetiapine. Despite her present decompensation, discussion with the clinicians who had previously treated her reveals that she has done well on haloperidol and thus she is restarted on her outpatient dose.

Over the next week, Ms. A begins to interact more appropriately with nursing staff and can make her needs known; however, conversations are still extremely brief and based primarily around her requests. Although the frequency of her distressed outbursts has

decreased, she is still responding to internal stimuli, loudly yelling and crying out at times. After 2 weeks, Ms. A still will not cooperate with her treatment team or social workers. She refuses to talk about planning her discharge, and often remains in bed for long periods during the day.

What would be your next step in treating Ms. A's psychotic illness?

- increase the haloperidol dose
- add a second antipsychotic
- add an antidepressant
- switch to a different antipsychotic

The authors' observations

As a class, antipsychotics lead to symptom reduction in approximately 70% of patients.¹ However, the degree of response can vary markedly between individuals; although some patients may experience almost complete resolution of symptoms, others are still markedly impaired, as in Ms. A's case.

continued

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Clinical Point

Although the practice is common, use of >1 antipsychotic does not significantly increase efficacy but increases risk of adverse effects

Table 1

Evidence for a role of estrogen in schizophrenia

Worsening of symptoms during low estrogen in phases: premenstrual phase of estrous cycle, postpartum, and during the menopausal transition

Later onset and less severe course of schizophrenia in women

Second peak of onset of schizophrenia during menopausal transition

Low estrogen levels in women with schizophrenia

Evidence of interactions between estrogen and the dopamine and serotonin systems

Improvement of symptoms in animal models of schizophrenia with administration of estrogen

Improvement of symptoms in patients with administration of estrogen or SERMs

SERMs: selective estrogen receptor modulators

Source: References 13,14

A substantial amount of literature suggests that although the practice is common, use of >1 antipsychotic does not significantly increase efficacy but increases risk of adverse effects, such as type 2 diabetes mellitus, metabolic syndrome, cognitive impairment, and extrapyramidal symptoms.²⁻⁴ One exception is augmentation of clozapine with a second antipsychotic, which in certain cases appears to offer greater efficacy than clozapine alone.¹ Practice guidelines and evidence generally do not support the use of multiple antipsychotics, but 20% of patients take >1 antipsychotic.^{5,6} Although antipsychotic polypharmacy may be appropriate for some patients, current literature suggests it is being done more often than recommended.

Clozapine is considered the most efficacious option for treatment-resistant schizophrenia.⁷ Because of Ms. A's history of recurrent hospitalizations, her extensive list of trialed medications, and her ongoing symptoms despite a sufficient trial of haloperidol, the treatment team gives serious

consideration to switching Ms. A to clozapine. However, Ms. A is not able to tolerate blood draws without significant support from nursing staff, and it is likely she would be unable to tolerate the frequent blood monitoring required of patients receiving clozapine.

Because many of Ms. A's symptoms were negative or depressive, including hypersomnia, psychomotor retardation, sadness with frequent crying spells, and reduced interest in activities, adding an antidepressant to Ms. A's medication regimen was considered. A recent systematic review and meta-analysis showed that adding an antidepressant to an antipsychotic in patients with schizophrenia had small but beneficial effects on depressive and negative symptoms and a low risk of adverse effects.⁸ However, Ms. A declined this option.

TREATMENT Adding long-acting haloperidol

Ms. A had previously achieved therapeutic blood levels⁹ with oral haloperidol. Data suggest that compared with the oral form, long-acting injectable antipsychotics can both improve compliance and decrease rehospitalization rates.¹⁰⁻¹² Because Ms. A previously had done well with haloperidol decanoate, 200 mg every 2 weeks, achieving a blood level of 16.2 ng/mL, and because she had a partial response to oral haloperidol, we add haloperidol decanoate, 100 mg every 2 weeks, to her regimen, with the intention of transitioning her to all-depot dosing. In addition, the treatment team tries to engage Ms. A in a discussion of potential psychological contributions to her current presentation. They note that Ms. A has her basic needs met on the unit and reports feeling safe there; thus, a fear of discharge may be contributing to her lack of engagement with the team. However, because of her limited communication, it is challenging to investigate this hypothesis or explore other possible psychological issues.



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Table 2

Raloxifene: An overview

Mechanism of action	Estrogen receptor agonist and antagonist
Dosing	Typical dose 60 mg/d. Can increase to 120 mg/d
FDA-approved use	Prevention and treatment of osteoporosis. Prevention of invasive breast cancer
Black-box warning	Increased risk of venous thromboembolism (NNH: 158). Increased risk of fatal stroke (NNH: 250)
Metabolism	Glucuronide conjugation
Excretion	Primarily in bile via feces, with small amounts excreted in urine
Time to steady state	6 weeks
Common adverse effects	Hot flashes, vaginal dryness, leg cramps
Contraindications	History of venous thromboembolic events (DVT, PE, retinal vein thrombosis)
Precautions	Immobilization Risk factors for thromboembolism (ie, CHF, active malignancy) Coronary heart disease History of hypertriglyceridemia on estrogen History of stroke or at increased risk of stroke (history of TIA, hypertension, atrial fibrillation, cigarette smoking)

CHF: congestive heart failure; DVT: deep vein thrombosis; NNH: number needed to harm; PE: pulmonary embolism; TIA: transient ischemic attack

Source: References 21-24

Clinical Point

Estrogen levels can influence the development and severity of symptoms of schizophrenia

Despite increasing the dosing of haloperidol, Ms. A shows minimal improvement. She continues to stonewall her treatment team, and is unwilling or unable to engage in meaningful conversation. A review of her chart suggests that this hospital course is different from previous ones in which her average stay was a few weeks, and she generally was able to converse with the treatment team, participate in discussions about her care, and make decisions about her desire for discharge.

The team considers if additional factors could be impacting Ms. A's current presentation. They raise the possibility that she could be going through menopause, and hormonal fluctuations may be contributing to her symptoms. Despite being on the unit for nearly 2 months, Ms. A has not required the use of sanitary products. She also reports to nursing staff that at times she feels flushed and sweaty, but she is afebrile and does not have other signs or symptoms of infection.

Can estrogen levels impact symptoms of schizophrenia?

- no, there is no known effect
- yes, low levels of estrogen worsen symptoms of schizophrenia
- yes, low levels improve symptoms of schizophrenia

The authors' observations

Evidence suggests that estrogen levels can influence the development and severity of symptoms of schizophrenia (*Table 1*,^{13,14} *page 48*). Rates of schizophrenia are lower in women, and women typically have a later onset of illness with less severe symptoms.¹³ Women also have a second peak incidence of schizophrenia between ages 45 and 50, corresponding with the hormonal changes associated with menopause and the associated drop in estrogen.¹⁴ Symptoms also fluctuate with hormonal cycles—women experience worsening symptoms during

Table 3**Patient characteristics to consider before starting raloxifene**

Peri- or postmenopausal woman
Diagnosis of schizophrenia or schizoaffective disorder
Incomplete response to antipsychotics
No history of venous thromboembolism
No history of stroke, transient ischemic attack, or other stroke risk factors
Minimal or nonsmoker

Clinical Point

Estrogen has been shown to directly impact both the dopaminergic and serotonergic systems

the premenstrual phase of the menstrual cycle, when estrogen levels are low, and an improvement of symptoms during high-estrogen phases of the cycle.¹⁴ Overall, low levels of estrogen also have been observed in women with schizophrenia relative to controls, although this may be partially attributable to treatment with antipsychotics.¹⁴

Estrogen affects various regions of the brain implicated in schizophrenia and likely imparts its behavioral effects through several different mechanisms. Estrogen can act on cells to directly impact intracellular signaling and to alter gene expression.¹⁵ Although most often thought of as being related to reproductive functions, estrogen receptors can be found in many cortical and subcortical regions of the brain, such as the hippocampus, substantia nigra, and prefrontal cortex. Estrogen receptor expression levels in certain brain regions have been found to be altered in individuals with schizophrenia.¹⁵ Estrogen also enhances neurogenesis and neuroplasticity, playing a role in learning and memory.¹⁶ Particularly relevant, estrogen has been shown to directly impact both the dopaminergic and serotonergic systems.^{15,17} In animal models, estrogen has been shown to decrease the behavioral effects induced by dopamine agonists and decrease symptoms of schizophrenia.¹⁸ The underlying molecular mechanisms by which estrogen has these effects are uncertain.

Given estrogen's potentially protective effects, clinical trials have explored the role of estrogen as an adjuvant to antipsychotics for treating schizophrenia. Studies have shown that estrogen can improve psychotic symptoms in patients with schizophrenia.^{19,20} However, because estrogen administration can increase the risk of breast and uterine cancer, researchers are instead investigating selective estrogen receptor modulators (SERMs).¹⁴ These medications have mixed agonist and antagonist effects, with different effects on different tissues. Raloxifene is a SERM that acts as an estrogen agonist in some tissues, but an antagonist in uterine and breast tissue, which may minimize potential deleterious adverse effects (*Table 2*,²¹⁻²⁴ *page 49*). Repeated randomized controlled trials have found promising results for use of raloxifene as an adjunctive treatment in peri- and postmenopausal women with schizophrenia, including those refractory to antipsychotic treatment.^{13,25-27}

TREATMENT Address symptoms

The treatment team takes steps to address Ms. A's perimenopausal symptoms. For mild to moderate hot flashes, primary interventions are nonpharmacologic.²⁸ Because Ms. A primarily reports her hot flashes at night, she is given lightweight pajamas and moved to the coolest room on the unit. Both bring some relief, and her hot flashes appear to be less distressing. The treatment team decides to consult Endocrinology to further investigate the feasibility of starting raloxifene (*Table 3*) because of their experience using this medication to manage osteoporosis.

What should be considered before starting a patient on raloxifene?

- smoking status
- cardiovascular risk factors
- cancer history
- current hormone levels

The authors' observations

Raloxifene is FDA-approved for treating osteoporosis and preventing invasive breast cancer.²⁹ Because it is an estrogen antagonist in both breast and uterine tissues, raloxifene does not increase the risk of uterine or breast cancer. Large studies have shown rates of cardiovascular events are similar for raloxifene and placebo, and some studies have found that raloxifene treatment is associated with improvement in cardiovascular risk factors, including lower blood pressure, lower low-density lipoprotein cholesterol, and increased high-density lipoprotein cholesterol.²⁹ Raloxifene does, however, increase risk of venous thromboembolism, including deep vein thrombosis and pulmonary embolism, and fatal stroke.^{29,30} Overall, the risk remains relatively low, with an absolute risk increase of fatal stroke of 0.7 per 1,000 woman-years (number needed to harm [NNH]: 250) and an absolute risk increase of venous thromboembolic events of 1.88 per 1,000 women-years (NNH: 158).³¹ However, raloxifene may not be appropriate for patients with independent risk factors for these events. Despite this, a large meta-analysis found a 10% decrease in mortality for patients taking raloxifene compared with those receiving placebo.³² Raloxifene also can cause hot flashes, muscle cramps, and flu-like symptoms.²⁹

Diagnosis of menopause and perimenopause is largely clinical, with hormone testing generally recommended for women age <45 in whom the diagnosis may be unclear.²⁸ Thus, Ms. A's vasomotor symptoms and absence of a menstrual cycle for at least

Related Resources

- Rosen H. Selective estrogen receptor modulators for prevention and treatment of osteoporosis. <http://www.uptodate.com/contents/selective-estrogen-receptor-modulators-for-prevention-and-treatment-of-osteoporosis>.
- Massachusetts General Hospital Center for Women's Mental Health. Raloxifene improves cognition in schizophrenia. <https://womensmentalhealth.org/posts/raloxifene-improves-cognition-in-schizophrenia>.

Drug Brand Names

Chlorpromazine • Thorazine	Paliperidone • Invega
Clozapine • Clozaril	Quetiapine • Seroquel
Fluphenazine • Prolixin	Raloxifene • Evista
Haloperidol • Haldol	Ziprasidone • Geodon

2 months were diagnostic of perimenopause; a 12-month cessation in menstrual cycles is required for a diagnosis of menopause.²⁸

OUTCOME Improvement with raloxifene

Because Ms. A is at relatively low risk for a thromboembolism or stroke, the benefit of raloxifene is thought to outweigh the risk, and she is started on raloxifene, 60 mg/d. Over the next 2 weeks, Ms. A becomes increasingly interactive, and is seen sitting at a table talking with other patients on multiple occasions. She spends time looking at fashion magazines, and engages in conversation about fashion with staff and other patients. She participates in group therapy for the first time during this hospital stay and begins to talk about discharge. She occasionally smiles and waves at her treatment team and participates more in the daily interview, although these interactions remain limited and on her

Clinical Point

Raloxifene may be considered an adjunctive treatment for peri- and postmenopausal women with schizophrenia

Bottom Line

The menopausal transition is a time of increased risk for women with schizophrenia. For peri- and postmenopausal women with schizophrenia, a selective estrogen receptor modulator, such as raloxifene, may be considered as an adjunctive therapy. Evaluate the risks and benefits of raloxifene, particularly the increased risk of thromboembolism, before starting this medication.

terms. She maintains this improvement and is transferred to a psychiatric facility in her home county for ongoing care and discharge planning.

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Clinical Point

As an estrogen antagonist in both breast and uterine tissues, raloxifene does not increase the risk of uterine or breast cancer